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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
10/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,826	VERFAILLIE ET AL.	
	Examiner	Art Unit	
	CHANG-YU WANG	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-13* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/09 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 8/18/09 is acknowledged. Claims 3 and 4 are cancelled. Claims 1 and 13 are amended. Claims 1-2 and 5-13 are pending in this application. Claim 12 is withdrawn with traverse (filed on 11/19/07) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/19/07.

3. Claims 1-2, 5-11 and 13 are under examination with respect to bone marrow and dopaminergic neurons in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this office action, has been overcome by Applicant's response.

5. Applicant's arguments filed on 8/18/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

6. The rejection of claim 3 under 35 U.S.C. 112, second paragraph, as being indefinite is moot because the claim is canceled.

The rejection of claims 7-8 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's arguments on p. 5-6.

Claim Rejections/Objections Maintained

In view of the amendment filed on 8/18/09, the following rejections are maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 5-9, 11 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO02/086073 (Studer et al., published Oct 31, 2002, cited in office

action mailed 10/18/07) in view of US2003/0211605 (Lee et al., published Nov 13, 2003, priority May 1, 2000). The rejection is maintained for the reasons made of record.

Claims 1-2, 5-9, 11 and 13 as amended are drawn to a method for inducing stem cells to differentiate into neuronal cells comprising a) culturing said stem cells with bFGF, b) culturing the cells of step a) with FGF8 and SHH, c) culturing the cells of step b) with BDNF and d) co-culturing the cells of step c) with astrocytes, wherein the cells are cultured according to steps a) through d) for at least seven days at each step. Dependent claims are directed to different stem cells.

On p. 6-10 of the response, Applicant argues that the claimed invention requires the sequential steps of culturing stem cells with neurotrophic factors and co-culturing the cells with astrocytes whereas Studer/Lee applied all of the growth factors at the same time on a specific committed cell type. Applicant argues that there is no motivation to alter the Studer and Lee's procedures by culturing for seven days at each step to practice the claimed invention. Applicant argues that at the end of the claimed procedures, the claimed method would not contain the same culture ES cells because the claimed method requires four steps and sequential addition of growth factors and thus the growth factors would act on four phenotypically discrete cell types while the factors in the cited references would act on one phentotypically discrete cell type. Applicant further cites Dr. Catherine Verfaillie's declaration (p.2 and the cited reference Snykers et al.) in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07.

It is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Further, there is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007).

In contrast to Applicant's arguments, the examiner asserts that the combined references do render the claimed invention obvious because the claimed method uses the same growth factors and same ES cells. In addition, the declaration under 37

CFR 1.132 filed 8/18/09 is insufficient to overcome the rejection of claim 1-2, 5-7, 9, 11 and 13 under 35 U.S.C. 103(a) based upon references WO02/086073 (Studer et al., published Oct 31, 2002, cited in office action mailed 10/18/07) in view of US2003/0211605 applied under 35 U.S.C. 103(a) as set forth in the last Office action because: first, the declaration fails to provide side-by-side comparisons to demonstrate that the claimed cell types or end products generated from sequential addition of growth factors in the instant specification are different from those that are exposed to the same growth factors as taught in the cited references. Second, the differentiated cells in the cited reference (Snykers et al. Toxicological science. 2006, 94: 330-341) are not relevant to the instant applications because they are differentiated into different cells and thus cannot be compared with stem cells differentiated into neurons. Thus, the declaration filed on 8/18/09 is insufficient to overcome the 103(a) rejection.

In addition, although the instant method recites adding bFGF, FGF8, SHH and BDNF sequentially, the claimed method is only directed to inducing neuronal differentiation not directed to specifically defined proportions of the specific types of neurons. It is noted that the claimed method and the cited references are directed to the same goal using the same materials. The claimed method is directed to inducing neuronal differentiation using the same growth factors (bFGF, FGF8, SHH and BDNF) and the same ES cells, which are taught by the cited references. Although the claimed method alters the way of adding growth factors, and phenotypical cell types may have different proportions during the recited culturing procedures, at the end of the steps, the

end result of neuronal differentiation is expected and to generate dopaminergic neurons. Note that

"The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." See MPEP 2144.07

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105USPQ 233, 235 (CCPA 1955)" See MPEP 2144.05-II

In addition,

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

In response to Applicant's arguments related to sequentially adding growth factors for at least 7 days in each step, the examiner asserts that the combined references of Studer and Lee do render the claimed procedures obvious because Lee teaches that addition of SHH and FGF8 at the early stages is less effective (see p. 9, [0126], in particular). In addition, Lee teaches that the CNS precursor cells (including CNS stem cells and embryoid cells/neurospheres) are expanded in the CNS proliferation medium in the presence of bFGF or EGF for about 6 to 7 days (see p. 9, [0123]-[0124], in particular). Lee also teaches that the culture medium may also be supplemented with SHH and FGF8 because SHH and FGF8 are more effective to increase the generation of dopaminergic neurons (see p.9, [0125], in particular). Moreover, Lee teaches that neuronal differentiation is induced by withdrawal of at least one neurological agent, such as bFGF in the culture medium in the presence of the

factors to enhance the generation of dopaminergic neurons for five to 6 days (see p. 9, [0128]; p. 14, example 5, in particular).

Furthermore, Studer teaches that in order to generate astrocytes, before adding SHH and FGF8 into the culture medium, the ES cells are proliferated and cultured in a culture medium in the presence of bFGF (see p. 5, paragraphs 16-17; p. 26, paragraph 78, in particular). Studer teaches that to enhance dopaminergic and serotonergic neurons, ES cells are cultured in the proliferation culture medium in the presence of FGF8 and SHH for 6-9 days (see p. 28, paragraph 85; p. 29, paragraph 86, in particular). Studer also teaches that expanded ES cells from stage IV are induced to neuronal differentiation in the culture medium in the presence of BDNF and in the absence of SHH and FGF8 for 4-10 days (see p. 26, paragraph, 78; p.29, paragraph 87, in particular).

Both Lee and Studer do teach the use of different growth factors separately because each different growth factor can enhance different cell populations. For example, Lee and Studer teach that bFGF can be used to expand ES cells, and FGF8 and SHH can be used to increase the generation of dopaminergic neurons. In addition, the culture medium in the presence of bFGF and in the absence of FGF8 and SHH can increase astrocyte generation. Further, the culture medium in the presence of BDNF and in the absence of FGF8 and SHH can induce neuronal differentiation. Thus, it would have been obvious to add different growth factors sequentially. The person would have been motivated to do so because each different growth factor can increase specific type cell populations. In this case, the addition of bFGF is to induce ES cell

expansion and can enhance astrocyte generation for neuronal survival. The addition of FGF8 and SHH to the expanded ES cells after the exposure of bFGF can enhance the generation of dopaminergic and serotonergic neurons. The addition of BDNF after the exposure of FGF8 and SHH can induce neuronal differentiation.

Moreover, although Studer and Lee do not explicitly teach at least 7 days for each step, the claimed procedures and incubation time for each step are obvious over the cited reference because the incubation time for each step is within or overlaps with the claimed incubation. In addition, as previously made of record, it is known in the art that neural cells (neural progenitor/stem cells) co-cultured with astrocytes can enhance neuronal survival and differentiation. Thus, it has been obvious to combine the teachings of Studer and Lee to achieve and practice the claimed invention because the results of dopaminergic and serotonerigc neuronal differentiation are expected. Note that

In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie*case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990), See MPEP 2144.05-I.

"a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)" See MPEP 2144.05-I.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105USPQ 233, 235 (CCPA 1955)" See MPEP 2144.05-II.

On p. 10 of the response, Applicant argues that Studer does not expose the factors to ES cells because the cells used in Studer express nestin. Applicant's arguments have been fully considered but they are not persuasive.

As previously made of record, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In addition, the examiner asserts that Studer does teach ES cells (see p. 1, in particular). Note that the instant claims fail to limit what specific markers are expressed in ES cells. In addition, it is noted that the expression of nestin has also been used as a stem cell marker in the art.

Taken together, the claimed method of sequentially adding growth factors to ES cells is obvious over the cited references because Lee and Studer do provide a motivation and an expectation of success to add growth factors sequentially. Lee and Studer teach that each different growth factor used separately can enhance different cell populations. For example, ES cells incubated with bFGF alone with no FGF8 and SHH will increase ES cell proliferation and increase astrocyte generation, and astrocytes have been shown to enhance neuronal survival. In addition, expanded ES cells incubated with FGF8 and SHH will increase the generation of dopaminergic and serotonergic neuronal lineage. Finally, ES cells treated with FGF8 and SHH and further incubated with BDNF without bFGF or FGF8 and SHH can be induced into

dopaminergic neurons. Thus, a skilled artisan would have been motivated and would have expected success to add growth factors sequentially to expand specific neuronal populations.

8. Claims 1-2, 5-11 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO02/086073 (Studer et al., published Oct 31, 2002, cited in office action mailed 10/18/07) in view of US2003/0211605 (Lee et al., published Nov 13, 2003, priority May 1, 2000) as applied to claims 1-7, 9, 11 and 13 above, and further in view of Song et al. (Methods in Mol. Biol. 2002. 198: 79-88). The rejection is maintained for the reasons made of record.

Claims 1-2, 5-11 and 13 as amended are drawn to a method for inducing stem cells to differentiate into neuronal cells comprising a) culturing said stem cells with bFGF, b) culturing the cells of step a) with FGF8 and SHH, c) culturing the cells of step b) with BDNF and d) co-culturing the cells of step c) with astrocytes, wherein the cells are cultured according to steps a) through d) for at least seven days at each step. Dependent claims 5-11 are directed to different stem cells.

On p. 11 of the response, Applicant argues that Song does not cure the deficiencies of Suder and Lee to reach the claimed invention. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, as previously made of record and for the reasons as set forth above, Studer and Lee do render the claimed invention of the claims 1-2, 5-11 and 13 obvious.

Although Studer and Lee do not teach multipotent adult progenitor cells and bone marrow as recited in instant claims 7-10, Song et al. teach a method of culturing and differentiating bone marrow and umbilical cord blood cells into neural progenitor cells and neurons in a DMEM/F12 medium comprising FGF-2/bFGF, EGF, transferrin, insulin, putrescine, progesterone, selenium, trans-retinoic acid, BDNF and NGF (see p. 80, in p articular). Song et al. also teach culturing human and mouse bone marrow and human umbilical cord cultures (p. 82-83). The bone marrow and umbilical cord blood cells encompass stem cells and nonhematopoietic progenitor cells from bone marrow are mesenchymal stem cells or bone marrow stromal cells as taught by Song et al. (p.79), which meet the limitations of multipotent adult progenitor cells (MAPCs) and bone marrow as recited in instant claims 7-10. Thus, it is obvious to differentiate stem cells that are derived from multipotent adult progenitor cells (MAPCs) and bone marrow into neurons by using the culture conditions of WO02/086073 and US2003/0211605.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 8 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This is a new matter rejection. The rejection is maintained for the reasons made of record.

On p. 12 of the response, Applicant argues that the recitation "cells that are not embryonic stem cells.....can differentiate into at least one cell type of each of the endodermal, ectodermal and mesodermal embryonic lineages" is not new matter because the limitation was recited in the parent application (US Patent No. 7015037) and the '037 patent was incorporated into 11/238234, 10467963 and the instant applications. Neither 11/238234 nor 10/467963 addresses such recitation as new matter. Applicant further cites Appendix D in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the instant specification only teaches

" 'MAPC' is an acronym for a multipotent adult progenitor cell. It refers to a non-embryonic stem cell that can give rise to cell lineages of all three germ layers upon differentiation. See PCT/US00/21387, published as WO 01/11011, and filed as U.S. Application Serial No. 10/048,757 (specifically incorporated by reference....." see p. 6 of the specification.

The incorporated reference 10/048757 only teaches "an isolated multipotent non-embryonic, non-germ cell line cell that expresses transcription factors Oct3/4, REX-1 and ROX-1" and also states that the cell may have the capacity to be induced to differentiate to form at least one differentiated cell type of mesodermal, ectodermal and endodermal origin" see p. 8-9 of the specification of 10/048757. Note that the scope of the cells that express specific markers (transcription factors) as in 10/048757 are different from that of the cells with no defined markers as recited in instant claims. Neither the instant specification nor the cited incorporated references teach the limitation "cells that are not embryonic stem cells, embryonic germ cells, or germ cells

and can differentiate into at least one cell type of each of the endodermal, ectodermal and mesodermal embryonic lineages." because the scope of the instant claims is not limited to specific cells that express specific transcription factors and thus is different from that of the instant specification and also from that of the cited incorporated references. Thus, the limitation of "cells that are not embryonic stem cells, embryonic germ cells, or germ cells and can differentiate into at least one cell type of each of the endodermal, ectodermal and mesodermal embryonic lineages" recited in instant claims was not clearly disclosed in the specification and claims as filed. The limitation recited in the present claims, which did not appear in the specification or original claims, as filed, introduces new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112. Note that

"Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." See MPEP §2173.05

Conclusion

10. NO CLAIM IS ALLOWED.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang,
October 15, 2009

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649